FRIEDENWALD (H.)

The Causation of Inflammation.

A REVIEW.

BY

HARRY FRIEDENWALD, A. B., M. D.,

Lecturer on Ophthalmology and Otology,
College of Physicians and Surgeons, Baltimore.

REPRINTED FROM

The New York Medical Journal

for July 8, 1893.

Reprinted from the New York Medical Journal for July 8, 1893.

THE CAUSATION OF INFLAMMATION.

*A REVIEW.**

By HARRY FRIEDENWALD, A. B., M. D.,

LECTURER ON OPHTHALMOLOGY AND OTOLOGY,
COLLEGE OF PHYSICIANS AND SURGEONS, BALTIMORE.

In surveying the works of ophthalmologists of recent years, it appeared to me that one, above all others, deserves the widest recognition and the most thoughtful attention.

The work I refer to is on *The Causation of Inflammation*, by Theodor Leber, professor of ophthalmology, formerly of Göttingen, now of Heidelberg.†

This work is the result of many years of labor. Portions of it have been published from time to time. Others besides Leber have been engaged at the same task. In this last published work the entire subject is reviewed and his results and those of others are considered in a thorough manner, known in German as *Kritik*. In my paper I shall

* Read as the chairman's report of the Section in Ophthalmology etc., before the Medical and Chirurgical Faculty of Maryland, April, 1893.

† *Die Entstehung der Entzündung und die Wirkung der Entzündungserregenden Schädlichkeiten nach vorzugsweise am Auge.* Angestellten Untersuchungen von Dr. Theodor Leber. Leipsic, 1891.

not name the various authors, but confine myself to the report of some important facts and conclusions. Many of these are not new, but are familiar to pathologists; still their repetition may be of use. The experiments were made, for the most part, on the eyes of rabbits and other animals.

The eye possesses many advantages for observing the processes of inflammation. Its transparent media enable us to see the gradual and minute changes. Some of its tissues being non-vascular, reduces the complex processes of inflammation to the most simple terms. It has also been found that there is very slight danger of secondary infection after careful experiments on the eye.

The great work had its beginning in a very interesting and rare case. A countryman whose eye had been injured with chaff was attacked with suppurative keratitis. The necrotic corneal tissue was filled with a variety of aspergillus (*A. fumigatus*). Experiments showed that this fungus was capable of causing similar inflammation in the cornea of living rabbits, into which it was introduced.

These were the first experiments with pure cultures of fungi, and they proved that certain forms were capable of development in previously healthy animal tissues and of producing suppurative inflammation without the aid of bacteria. Further experiments proved that different fungi were very unlike in these properties or in the intensity of their action, some varieties being incapable of development at the body temperature, some finding the cornea and other tissues unsuitable soil. It has also been found that different organs are affected to a very varying extent by fungi injected into the blood-vessels, and that, moreover, different animals show greater or less predisposition to their action. Non-vascular tissues offer the best culture ground.

The introduction of pure cultures of *Aspergillus fumi-*

gatus into the cornea is followed by keratitis manifesting itself the next day. There is some conjunctivitis, which gradually increases, and the corneal wound is slightly infiltrated. The infiltration, at first limited to the corneal wound, gradually increases in density and size, and the epithelial covering is lost. The peripheral part of the cornea becomes somewhat hazy. About this time (third or fourth day or later) a crescentic or circular infiltration rapidly appears around the primary lesion. This is opaque, sharply defined, especially on its inner border, narrow, and stationary. Its outer border passes over into the diffuse haziness of the periphery of the cornea. Between the circular infiltration and the central lesion there is a larger or smaller area which at first is perfectly or almost clear. Later on the central infiltration increases and reaches the circular zone, and the epithelial layer within this area is lost.

In the mean time there is considerable exudation in the anterior chamber, beginning with a deposit upon the inner surface of the cornea beneath the primary infiltration, frequently similar to the circular corneal infiltration, but somewhat smaller, and a fibrinous deposit on the margin of the pupil and in the pupillary opening. On the anterior surface of the iris, especially below and at the bottom of the anterior chamber, there is a purofibrinous deposit.

The growth of the fungus is limited to the area inclosed in the circular zone, which acts as a line of demarcation; with few exceptions, the fungus did not enter the anterior chamber, Descemet's membrane offering too much resistance to its progress.

After five or six days the inflammation abated; at the same time there was a development of a vascular zone, spreading from the conjunctiva over the surface of the cornea and sometimes extending to the circular infiltration. The area within the circular zone, which has become puru-

lent and softened, is thrown off either entire, causing perforation of the cornea, or partially in some milder cases, producing a deep ulcer, and this is followed by cicatrization.

If we now follow the fate of the fungi which were introduced into the corneal substance either in the form of spores or of a developed mycelium, we find that they rapidly grow through the corneal substance in all directions, without any relation to its structure, forming a mycelium especially dense at the border of the growth. The growth is, however, as already stated, always limited to the area inclosed by the circular infiltration.

The minute changes in the cornea are no less interesting than those visible to the naked eye. The first consist in a loss of the epithelium and the endothelium above and below the growth and a superficial infiltration of leucocytes under the margin of the epithelial defect—to a slight depth —and in the epithelial layer near the margin. Rarely are they found entering along the fungous threads or even surrounding them. The periphery of the cornea is infiltrated with leucocytes; they are densest at the edge of the cornea and gradually diminish toward the center. The circular infiltration likewise consists of leucocytes, which here are closely packed between the fibers of the corneal tissue. In this zone they are so closely placed that their edges can not be seen, but at the margin they appear drawn out and distorted in their efforts to enter the narrow spaces. At the inner edge of the zone the infiltration suddenly ceases and neither leucocytes nor even corneal corpuscles are to be seen within. The zone of infiltration usually pervades all the layers; sometimes it does not reach the deepest one, and then it is seen to become closer in the deeper layers and perhaps, forming a continuous layer, surround the central infiltration from behind.

Besides the infiltration of leucocytes, there is an exudation of fibrin into the conjunctival and subconjunctival tissue about the cornea and into the cornea to the circular infiltration.

There is also an abundant production of pus and fibrin in the aqueous humor. It is important to remember that this purulent collection in the anterior chamber is formed very early—long before the fungous growth has reached the deepest layers of the cornea.

The iris and ciliary body show some infiltration with leucocytes, mostly on the anterior surface of the iris (nearest the cornea), and especially prominent near the angle of the anterior chamber.

In the further course the fungi are found to cease growing and the central area becomes more and more infiltrated with pus corpuscles. In these areas the corneal structure disappears entirely, and even the fungi are destroyed. The subsequent steps were mentioned above. In the mildest cases, in which the spores did not germinate at all or only very late, the inflammatory symptoms were very much slighter, but they were always present. In these cases there was an abundant infiltration of leucocytes where the spores had been introduced, and these were either filled with spores or were spread along the course of the developed threads in the form of a cloak. In a short time the enveloped threads could not be found, having been destroyed by the leucocytes. The spores which did not germinate gradually disappeared. The reason for the great difference in their action from those described above lay in their retarded development.

I have described this form of inflammation so minutely because I shall have to revert to it, and I shall be able to avoid lengthy descriptions in other forms by referring to this.

In the anterior chamber the *Aspergillus fumigatus* produced violent inflammation, but it developed a mycelium only in the membrane of Descemet of the cornea and in the anterior capsule of the lens. In the latter situation it produced no evident inflammatory reaction within the lens; the only change consisted in necrosis of the lenticular epithelial cells. The growths on the cornea produced a dense infiltration of leucocytes in the deep layers of the cornea corresponding to the part of Descemet's membrane affected. There was absolutely no growth of the fungus on the iris. This was covered with a thick layer of fibrinous exudation. In other words, the fact may be stated that the fungus develops in non-vascular tissues, but that it can not grow on those that are vascular. In the vitreous there was abundant development of the growth with violent symptoms of inflammation; the purulent infiltration extended to the retina and even into the anterior chamber. As in the cases of corneal infection, it was seen that the effects went far beyond the limits of the growth itself.

Leaving the class of the fungi and passing over to certain bacteria, we find that the introduction of pure cultures into the cornea produces symptoms very similar to those described above, due to the aspergillus, and that they also are capable of development in this soil. The early appearance of purulent exudation in the anterior chamber, besides other signs, shows that bacterial inflammation also spreads beyond the area occupied by the bacteria. It is especially interesting to note that this purulent collection, known as *hypopyon*, is free from germs, and is therefore due only *indirectly* to their presence in the cornea. It is also important to learn that the leucocytes forming the collection are not derived from the corneal infiltration at all, as is usually believed, but from the neighboring vascular parts—the iris and ciliary body. The consideration of the

changes constituting the foregoing forms of inflammation has shown that within a definite area around the growths there is necrosis of the tissue elements, and that beyond this there is infiltration with leucocytes.

In the corneal inflammations it was seen that the infiltration was twofold: firstly, slight infiltration beginning in the wound, and, secondly, an intense infiltration in the form of a limiting circle. Both depend upon the migration of leucocytes into the cornea, the former being derived from the contents of the conjunctival sac, the latter from the vascular tissues surrounding the cornea. In cases of slowly growing fungi the central infiltration may exist alone and become so great as to surround the separate threads of the growth in the form of a mantle.

The only explanation for the extensive action of micro-organisms is, that they produce by their growth certain soluble, diffusible, and poisonous substances, which in more concentrated forms produce necrosis of the tissue where they are formed, and which, reaching the neighboring blood-vessels in more diluted amounts and acting upon them, cause inflammatory hyperæmia, exudation, and emigration of leucocytes.

It was evident that the *leucocytes were attracted toward the seat of the micro-organisms.* In the cornea this was very apparent in the area between the periphery and the circular zone of infiltration. The reason that they proceeded no further than the circular band of infiltration—indeed, the reason that this band was formed—lay in the fact that here the concentration of the poison became too great and paralyzed them.

In these experiments the question arises as to what prevents the growth and the continued spread of the organisms. It was found under certain circumstances, especially when the inflammatory action was slight, that micrococci

and spores found their way into the interior of the leucocytes. This is due to a process known as *phagocytosis*—the taking up by leucocytes of small particles into their interior. How much this process interferes with the progress of the micro-organisms can not be stated, but it is probable that it is not important. Perhaps the reason lies in some property of the inflammatory exudate that is detrimental to their growth.

It is to the leucocytes that the most important work must be ascribed—namely, that of forming the line of demarcation and of separating the necrotic portion and causing it to be thrown off.

The experiments on the effects of the introduction of micro-organisms into various parts of the eye were followed by another series to determine the results of the introduction of their chemical extracts. Extracts of fungi, even of some which in themselves are incapable of producing any considerable inflammation, cause necrosis of a larger or smaller area of tissue and purulent infiltration beyond it. The same can be said of extracts of putrefied substances. The inflammation in these cases is similar to that produced by living organisms, but is less intense, owing to the fact that but small quantities could be introduced, that they were rapidly absorbed, and that they were not reproduced as they are when the living organisms lie in the tissues. Injections of boiled *Staphylococcus aureus* into the anterior chamber are followed by the most intense inflammation. But the course differs markedly from that produced by similar injections of the living organisms. The latter is a progressive inflammation which gradually destroys the whole eyeball. The former intense inflammation subsides after a certain time and ends in complete healing. Whenever the amount of injected material was sufficient, the inflammation was accompanied by the rapid pro-

duction of a large perforation of the sclerotic coat at the angle of the anterior chamber. This was due, it is believed, to the constant filtration through the angle of the anterior chamber and the consequently greater action of the poison at this part. There was a large amount of purofibrinous exudation in the anterior chamber, often filling the entire cavity, but hypopyon was found only in the most severe cases. (In these cases, too, the entire cornea became anæsthetic.) And yet, as stated above, this condition would pass away with absorption of all or of most of the exudation, and finally even a return of the transparency of the cornea. (This was preceded by vascularization of its periphery and a subsequent disappearance of the blood-vessels.)

The separation of the active chemical substance in solution from the boiled micrococci was a very difficult problem, but was finally solved. From the solution the dried crystalline substance was at last obtained. It is known as *phlogosin*. This substance causes necrosis and intense inflammation even of the uninjured conjunctiva. Introduced into the anterior chamber, it produced the most violent inflammation within a few hours, extending to the conjunctiva and even the eyelids.

Accepting the fact that the inflammatory action of micro-organisms depends upon chemical substances which they produce, the next question that arises is whether other chemical substances have like properties. It is not long since it was denied that chemical substances could produce suppurative inflammation. This was based upon the results of injections of certain substances, such as croton oil, which in most cases produced inflammatory œdema and exudation of fibrin only; though I wish to mention here that our former fellow-townsman, Professor Councilman, had shown that under proper conditions sterilized croton

oil would produce suppuration. Furthermore, we must bear in mind that there is no essential difference between suppurative and non-suppurative inflammation. In both there is emigration of leucocytes, and suppuration depends only upon its degree.

Among the many chemical substances examined were various metals, such as iron, copper, mercury, lead, silver, gold; besides these there were glass, carbon, arsenious acid, etc., of inorganic substances, and organic substances, such as croton oil, oil of turpentine, cantharidin, jequirity, indigo, uric acid, etc., and finally oil, starch, and parts of animal tissues. These were introduced into the anterior chamber (either directly or inserted in minute glass tubes, open at one end), into the vitreous, and into the cornea.

In all cases it was shown that the substances were pure and free from bacteria, and the eyes were afterward examined carefully to determine that no subsequent infection had occurred. Each substance seemed to act in a manner peculiar to itself. But all caused greater or less inflammation. It is impossible to give even an abstract of all these experiments. I shall confine myself to the results obtained in a very few, which will serve as examples, and to the general conclusions.

The introduction of sterile mercury was followed by suppurative exudation without considerable inflammatory reaction. I need scarcely repeat that in all experiments there were numerous examinations, which showed that there was no infection. About twelve hours after a drop of mercury was injected into the anterior chamber it was covered with pus. The purulent collection gradually increased. The cornea later on became vascular in that part where the purulent mass lay against it. Finally the cornea became purulent and softened at some point; perforation

would occur, and the anterior chamber would be emptied of its contents. Then recovery took place. Injected into the cornea in fine globules, it was found to produce severe inflammatory reaction. The globules were surrounded by a purulent deposit, and in one case where the drop was larger there was a distinct circular infiltration.

Bits of sterilized copper introduced into the anterior chamber acted in a similar manner. Suppuration began in about fifteen hours; but this involved only the part occupied by the foreign body. The rest of the iris was apparently normal. In a few days the collection of pus would reach the upper margin of the pupil. There was vascularization of the cornea, which finally covered the part over the purulent collection. If the anterior chamber was emptied, the symptoms would rapidly subside and recovery would take place. If not, there would be spontaneous diminution of the inflammation. The purulent collection would decrease. The corneal and conjunctival congestion would disappear, but the foreign body would usually work its way gradually out through the cornea. Copper acted in a very curious way when introduced partly into the lens so as not to be in contact with the vascular iris. In this case it produced very slight reaction. It was subsequently found that the action of copper was violent only when in contact with vascular tissue.

As an example of another mode of action let me refer to the experiments with arsenious acid. This produced extensive necrosis, but only slight suppurative reaction, and this at quite a distance from the seat of operation. Gradually as the acid became absorbed the infiltration came nearer. It was evident that the substance acted in a poisonous manner upon leucocytes even at a great distance. Introduced into the anterior chamber, it was seen almost unchanged for several days, without any infiltration or scarcely

any fibrinous exudation in its neighborhood. After several days only was there beginning suppurative exudation, and this occurred on the opposite side of the iris at the most distant point; later on there was exudation nearer the body.

In order to show the action of what are considered inert substances let me mention that of gold. In the anterior chamber pieces of gold produced no effect visible to the naked eye; but even after a few weeks the microscopic examination revealed proliferation of the endothelium, the formation of giant cells, and emigration of leucocytes. In the vitreous the effects were still more evident.

Having demonstrated that the above chemical substances, both the active and those otherwise considered inert, produce inflammation of different degrees and of different kinds, we are led to inquire in what manner and by what means this is accomplished. As in the case of inflammation due to micro-organisms, it was found that these substances showed effects through a much larger space than that they occupied—in other words, that they acted at a distance. This forces us to the conclusion that they must become partly dissolved in the animal fluids, and pass by diffusion to the neighboring parts. This could be directly proved in certain cases, as, for instance, with copper; it was demonstrated that neighboring tissues contained traces of this metal. Substances which are usually considered insoluble —such as gold, silver, glass—likewise show distant action, and the conclusion stated before can not be denied. They must be soluble to a very slight degree, and, furthermore, very small quantities of these solutions must suffice to produce inflammation. Solutions of mercury, copper, or lead salts are very poisonous, while iron is found as a normal ingredient in the animal body. The first metals named are very slightly soluble in the animal fluids, while the latter

is much more easily soluble. It is therefore very interesting to observe that the former excite considerable inflammation while the latter is almost harmless.

Oily substances which are insoluble in water are partly emulsified and are carried to neighboring parts in the form of fine particles. Whether in the form of an emulsion or of a solution, the above substances produce necrosis in their neighborhood and inflammatory reaction beyond by acting as irritants to the tissue elements. Substances which produce great inflammatory reaction must therefore be considered as cell poisons, which in weak concentration act as the excitants of inflammation.

Very inert substances act as excitants only and cause processes which lead to their elimination or encapsulation. It is conceivable that the various substances act in a different manner, and that this accounts for the differences in the forms of the inflammation produced.

A most interesting series of experiments consisted in the introduction of finely powdered substances into the anterior chamber and vitreous. They were either injected or placed in minute glass tubes and thus inserted. Among the substances experimented with were gold, platinum, cinnabar, sulphate of barium, and pure powdered carbon. In all the cases there was greater or less emigration of leucocytes from a distance, and the fine particles were partly taken up into their interior. There was also increased exudation of fibrin.

It is not conceivable that these substances acted purely in a mechanical way, for their action did not confine itself to their immediate neighborhood. Furthermore, the little tubes which contained these substances became filled to a greater or less extent with pus cells, while empty tubes produced but the slightest reaction. The action of the powdered substances, as in the case of gold, was much more intense than that of the solid pieces.

Leber holds that here too we must consider it a chemical action, and that these substances are not absolutely insoluble; and also that their solubility is increased by being in the form of powder, which has an infinitely greater surface exposed than the solid substances. The greatest difficulty which this view encounters is in the case of pure carbon; Leber is unable to give any hypothesis for its solubility. I would venture the hypothesis that the surface attraction of this substance may account for its action.

Leber's work offers further strong proof of the truth of Cohnheim's theory, that pus cells are derived by emigration from neighboring vessels. I can not refrain from citing certain experiments which bear strongly on this point, and show conclusively that the tissue cells are of secondary importance in the formation of pus. He introduced dead sterile corneas into the abdomen of rabbits. Some of these corneas were first injected with small amounts of sterile putrefactive fluid, just, as mentioned above, had been done with living eyes. Those that contained this inflammation-producing fluid showed the same characteristic forms of purulent infiltration when taken out of the abdomen as described above—slight infiltration at the seat of injection and a ring of infiltration at a definite distance from it. The non-injected dead corneas when taken out of the rabbit's belly showed but slight general infiltration, as would have been expected, for these also act as foreign bodies. The experiment was made additionally instructive by the fact that most pus cells of the circular infiltration contained pigment granules which were derived from the narrow pigment zone found around the cornea, which had been taken up in their course through this part. The pus cells of the central infiltration were entirely free, and this showed that they had come from without directly into this part without traversing the periphery.

According to Leber, the same attraction which brings leucocytes from a distance causes them to surround the fine particles and to take them into their interior, the process mentioned above as *phagocytosis.* In this action various powdered substances are not at all equal. The whole process by which the leucocytes are attracted through chemical irritation he terms *chemotaxis.*

REASONS WHY

Physicians Should Subscribe

FOR

The New York Medical Journal,

EDITED BY FRANK P. FOSTER, M. D.,

Published by D. APPLETON & CO., 1, 3, & 5 Bond St.

1. **BECAUSE:** It is the *LEADING JOURNAL* of America, and contains more reading matter than any other journal of its class.
2. **BECAUSE:** It is the exponent of the most advanced scientific medical thought.
3. **BECAUSE:** Its contributors are among the most learned medical men of this country.
4. **BECAUSE:** Its "Original Articles" are the results of scientific observation and research, and are of infinite practical value to the general practitioner.
5. **BECAUSE:** The "Reports on the Progress of Medicine," which are published from time to time, contain the most recent discoveries in the various departments of medicine, and are written by practitioners especially qualified for the purpose.
6. **BECAUSE:** The column devoted in each number to "Therapeutical Notes" contains a *résumé* of the practical application of the most recent therapeutic novelties.
7. **BECAUSE:** The Society Proceedings, of which each number contains one or more, are reports of the practical experience of prominent physicians who thus give to the profession the results of certain modes of treatment in given cases.
8. **BECAUSE:** The Editorial columns are controlled only by the desire to promote the welfare, honor, and advancement of the science of medicine, as viewed from a standpoint looking to the best interests of the profession.
9. **BECAUSE:** Nothing is admitted to its columns that has not some bearing on medicine, or is not possessed of some practical value.
10. **BECAUSE:** It is published solely in the interests of medicine, and for the upholding of the elevated position occupied by the profession of America.

Subscription Price, $5.00 per Annum. Volumes begin in January and July.